**Title:** “Proteostasis as a Therapeutic Target for Treating Heart Disease”

**Abstract:** Most pathologies are either caused by, or exacerbated by the accumulation of misfolded proteins, which aggregate and become toxic; this proteotoxicity causes damage and thus impairs cellular and organ function. Such proteotoxicity arises from imbalances in protein homeostasis, or proteostasis, which is often associated with increased protein misfolding. In all mammalian cells such protein misfolding is sensed by several stress response systems, including the unfolded protein response (UPR). The UPR was originally found to be activated by misfolded proteins in the endoplasmic reticulum (ER), but is now known to be responsive to misfolded proteins in additional cellular locations. Our research has focused on the ER UPR in the cardiac myocytes as a potential therapeutic target for heart diseases, such as those related to myocardial infarction, as well as pathological cardiac hypertrophy, dilated cardiomyopathy and heart failure. We found that one arm of the UPR that involves the transcription factor, ATF6, protects the heart from many cardiac pathologies. Our molecular genetic studies in mice have shown that the gene programs regulated by ATF6 differ depending on the pathology; moreover, deleting ATF6 specifically in cardiac myocytes exacerbates cardiac pathology, demonstrating a key role for ATF6 in maintaining cardiac structure and function. We also found that overexpressing ATF6 is protective by virtue of its abilities to increase expression of proteins that rebalance proteostasis by decreasing protein misfolding.

Our recent work has focused on identifying small molecule activators of ATF6, which would conceptually boost the protective effects of endogenous ATF6 in the heart. We have identified several candidate small molecule activators of ATF6, which we have shown to decrease misfolded protein accumulation in cardiac pathologies in mice, leading to a remarkable protection from proteotoxic damage and to a preservation of heart function. Since ATF6 is expressed in other cell types, we have explored the effects of small molecule activators of ATF6 in other disease models, showing, for example, that they are effective in decreasing damage and preserving function in mouse models of cerebral ischemia. We are currently developing ATF6 activators for use in larger animal studies as a critical next step in adapting them for potential clinical use.